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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,910	10/20/2004	Kazushi Imai	TAN-345	4544

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EXAMINER	
CHO, DAN SUNG C	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,910	IMAI, KAZUSHI	
	Examiner	Art Unit	
	Dan-Sung C. Cho	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed 10/20/2004. Currently, claims 1-4 are pending.

Priority

2. This application is a 371 of PCT/JP03/05358 filed on 4/25/2003 and claims benefit of Japan application 2002-130883 filed on 5/2/2002. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 5/2/2002.

Claim Rejections - 35 USC § 112- Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

5. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of

direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

6. The claims are drawn to a method of detecting rheumatoid arthritis (RA) by detecting upregulation of WNT10B or by detecting, in parallel to WNT10B, inhabitation of one of the five known FRP mRNAs expression in synovial fluid, synovial tissue or in peripheral blood. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

7. The art teaches synovium can be used to detect specific mRNAs using RT-PCR technique. Synovium contains a unique population of synovial lining cells in RA and osteoarthritis (OA) that appear to be activated in Wnt signaling phenotypes (Nakamura et al., 2005, American Journal of Pathology, 167:97-105, page 97, right column, paragraph 2). However, whether the detection of the presence of WNT10b mRNA and one of the 5 known FRP mRNAs in samples with no active organogenesis such as peripheral blood is not known in prior art. Peripheral blood cells may represent cells that have gone thorough organogenesis and therefore may not express WNT10b and FRPs. In addition, compared with normal tissues, real-time PCR revealed that mRNA levels of Wnt-10b in OA cartilage and RA synovium and FRZB, an FRP, in OA synovium and RA cartilage were significantly down-regulated compared to normal tissues. The levels of Wnt-10b and FRZB (FRP) between OA and RA cartilage and synovium do not appear

to significantly change (Nakamura, page 99, Figure 1 and page 102, right column, paragraph 1).

Guidance in the Specification.

8. The specification provides no evidence that the upregulation of WNT10B expression in synovial fluid, synovial tissue and in peripheral blood. The specification merely discloses of RT-PCR comparisons in 5 RA and 4 OA tissues and not RA to normal tissues. Therefore "upregulation" of expression of WNT10B in claims 1 and 2 is not enabled. Upregulation of WNT10b compared to OA is disclosed in the specification but not any other comparisons such as WNT10b mRNA level between RA and normal tissues. The specification also discloses RT-PCR detection of WNT10B and FRP1-5 using synovium, not peripheral blood. Because the expression of WNT ceases after completion of organogenesis (specification, page 2, paragraph 3, lines 26-29) whether WNT mRNA expression in peripheral blood can be detected is not certain. Table 2 illustrates results for WNT10B and FRPs for (+) presence or (-) absence. This is not upregulation or inhibition. Upregulation would encompass a quantitative change. Figure 1 illustrates expression of 4/5 and 1/4 WNT10B in RA and OA, respectively. It is noted this cannot be construed as over expression because no control (normal) to which to compare the intensities is disclosed. The specification also discloses WNT10b is specifically localized to synovial surface cells and endothelial cells in RA tissues while FRP1 is expressed in all of synovial cells (page 3, lines 3-10). The specification does not provide peripheral blood expression of WNT10b and FRPs.

9. Claim 3 and 4 reciting "inhabitation" is interpreted as "inhibition" of expression of FRP. Analysis of FRPs disclosed in the specification is between RA and OA synovium. There is no analysis of normal tissue or the amount of FRP expression in normal tissue in the specification. The specification does not disclose detection of FRPs in synovial

fluid, synovial tissue and in peripheral blood. Table 2 also illustrate not all FRPs are detected in the same manner. As the specification states (page 3, line 13) it merely discloses a trend of presence or absence of WNT10B and FRP1 in synovium. Therefore the specification does not provide guidance to detect upregulation or inhibition of WNT10b and FRPs mRNA. The specification also fails to disclose the comparison between peripheral blood samples of RA and other samples such as normal blood sample.

10. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Working Examples

11. The specification has no working examples of detecting RA by detecting upregulation of WNT10b and inhibition of FRPs in synovial fluid, synovial tissue and in peripheral blood, but rather discloses a trend toward RA having more cases of WNT10b expression and less of FRP1 RT-PCR positive synovium samples when compared to OA. Because the specification does not disclose the pattern of WNT10b and FRPs in normal samples, it fails to set a standard of how the detection result of RA can be used. In addition because of the limited number of samples disclosed in the specification where 5 RA and 4 OA samples were analyzed, the trend between RA and OA cannot be established with certainty. RA sample 4 and OA sample 8 in Table 2 appear to be more closely related to each other than to clinical classification of RA and OA, for example.

Quantity of Experimentation

12. The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied such as comparative studies of RA and normal (and not RA and OA as disclosed in the specification) of WNT10b, and any FRP1, 2, 3, 4, or 5 in joint synoivial fluid, synoivial tissues and peripheral blood.

13. First, whether peripheral blood can be used to detect WNT10b and any of FRP1, 2, 3, 4, or 5 needs to be established. Because peripheral blood is terminally differentiated and does not undergo active organogenesis, the detection of WNT10b and FRP1 would require significant quantity of experimentation to determine whether the expression pattern in blood is correlative with synovium.

14. Searching the specification does not disclose the use of control tissues. A significant number of normal and RA samples from synovium and peripheral blood samples must be compared to determine if WNT10b and any FRP1, 2, 3, 4, or 5 have either upregulation and inhibition of expression levels. Because the specification discloses only presence or absences of WNT10b and FRP mRNAs, a large number of samples are needed to be compared to determine what level of detection encompasses upregulation and inhibition between RA and normal samples. The skilled artisan would be required to perform additional experimentation to determine the level of upregulation. The results of the analysis are unpredicted and undue.

15. Of the five FRP mRNAs analyzed only FRP1, 2 and 4 appear to have more RT-PCR positive samples in RA than OA. The difference is small: 2/4 positives in OA vs. 1/5 positive in RA for FRP2 for example. Because of small sample sizes (5 RA, 4 OA and no normal) and no example of Normal tissue disclosed in specification, whether RA has inhibition of FRP 1, 2, 3, 4, or 5 mRNA expression compared to normal in synovium and peripheral blood needs to be determined through a large set of experimentation to

determine statistically significant expression level variations of FRP mRNAs levels. Since not all of the FRPs have the same presence of expression, it would be similarly unpredictable what level of expression they would have.

16. Because claims are drawn to upregulation or inhibition of WNT10b and FRP mRNAs, the levels of the mRNAs must be determined through experimentations such as quantitative PCR where levels of the mRNAs can be determined. The RT-PCR in the specification disclosed presence or absence of the mRNAs, not upregulation and inhibition.

17. This would require significant of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

18. The level of skill in the art is deemed to be high.

Conclusion

19. In the instant case, as discussed above, in a highly unpredictable art where the complex Wnt/Fz signaling may be involved in the etiology of RA so that diagnosis of RA can be made by detecting Wnt/Fz pathway mRNAs, the applicant disclosed no definition of upregulation and inhabitation of WNT10b and FRPs, respectively, to enable a skilled artisan in the art to make and use the invention. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized.
Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence

of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. The terms "upregulation" in claims 1-2 is a relative terms which renders the claim indefinite. The term "upregulation" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

22. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term “inhabitation” in claims 3 and 4 is used by the claim to mean “inhibition”, while the accepted meaning is “living or being present.” Applicant is reminded no new matter may be added.

23. Claims 1-4 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The preamble states that the method is for detecting rheumatoid arthritis but the final process step is detecting of upregulation of expression of WNT10B. Therefore the claims are unclear as to whether the method is a method of detecting rheumatoid arthritis or WNT10B upregulation.

24. Claims 3 and 4 are indefinite over the recitation FRP. It is unclear what is encompassed by FRP. FRP 1, 2, 3, 4, and 5 mRNAs are known in the art and it is not clear in claims 3 and 4whether the claims are limited to these 5 FRPs or whether any frizzled related protein is encompassed by the instant claims.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

26. The claims are drawn to methods for detecting RA by analyzing WNT10B and FRP. Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that Vas-

Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In The Regents of the University of California v. Eli Lilly (43. USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA. . .' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention.

27. In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. With respect to claims 1 and 2 which encompass detection of “at least the upregulation of expression of WNT10B” the current claims encompass a large genus of nucleic acids which comprise any WNT10B, which encompasses all splice variants and mutants. Similarly, with respect to claims 3 and 4 which encompass “inhabitation of expression of FRP”, the current claims encompass a large genus of nucleic acids which comprise any FRP, which encompasses, FRP1-5 and any frizzled related proteins. The genus includes an enormous number of variants, and combinations for which no written description is provided in the specification. This large genus is not represented in the specification.

28. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, "FRP" alone is insufficient to describe the genus. One of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one class of this genus, FRP1-5, is not representative of the variants of the genus and is insufficient to support the claim.

Conclusion

29. Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

30. Claims1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Sen et al., (Sen et al., 2000, PNAS, 97:2791-2796). Sen teaches detection of Wnt10b by RT-PCR in 5 RA and 5 OA synovial tissue samples, where 3/5 RA and 2/5 samples show Wnt10b signal. Because more RA samples show positive Wnt10b than OA samples, the claims are broadly construed to encompass this since RA has upregulated Wnt10b

expression. Claims 3 and 4 are directed to FRP which is broadly interpreted as any protein that is related to frizzle. Therefore FRP encompasses frizzle family protein including frizzle2 and frizzle 5. Sen teaches RT-PCR detection of fz2 and fz5 along with Wnt10b. Therefore Sen teaches each of the limitations of claims 1-4, namely detection by RT-PCR of Wnt10b and frizzled related protein simultaneously to detect whether a person has RA.

Conclusion

31. **No claims allowable over the art.**
32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.
33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.
34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). The Central Fax Number for official correspondence is (571) 273-8300.

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